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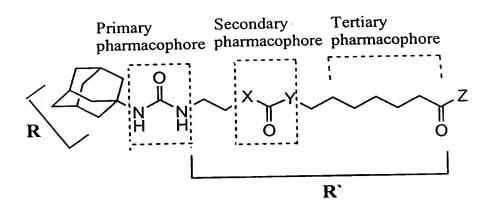
Applicant: Bruce D. Hammock et al Title: IMPROVED INHIBITORS FOR THE SOLUBLE EPOXIDE HYDROLASE

Sheets 1 of 11 Attorney Docket: 02307W-131010US

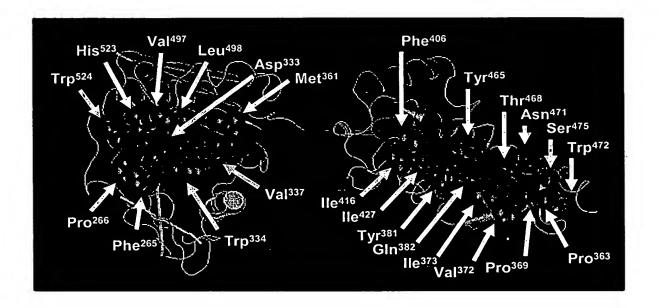
Figure 1

X: NH, O, or CH₂

R and R`: alkyl or aryl groups



Applicant: Bruce D. Hammock et al Title: IMPROVED INHIBITORS FOR THE SOLUBLE EPOXIDE HYDROLASE Sheets 2 of 11 Attorney Docket: 02307W-131010US



Applicant: Bruce D. Hammock et al Title: IMPROVED INHIBITORS FOR THE SOLUBLE EPOXIDE HYDROLASE Sheets 3 of 11 Attorney Docket: 02307W-131010US

Figure 4

| Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238) | MTLRGAVFDLDGVLALPAVFGVLGRTEEALAL RGLLNDA MALRVAAFDLDGVLALPSIAGVLRHTEEALAL RDFLLGA MALRVAAFDLDGVLALPSIAGAFRRSEEALAL RDFLLGA M | 40 40 40 22 |
|---|---|--------------------------|
| Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238) | FQKGGPEGATTRLMKGEITLSQWIPLMEENCRKCSETAKV FQMKFPEGPTEQLMKGKITFSQWVPLMDESCRKSSKACGA YQTEFPEGPTEQLMKGKITFSQWVPLMDESYRKSSKACGA NIWCVGQEGPSQEDTDTIHTSEWVPLMDESYRKSSKACGA | 80 80 80 62 |
| Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238) | CLPKNFSIKEIFDKAISARKINRPMLQAALMLRKKGFTTA SLPENFSISEIFSQAMAARSINRPMLQAAAALKKKGFTTC NLPENFSISQIFSQAMAARSINRPMLQAAIALKKKGFTTC NLPENFSISQIFSQAMAARSINRPMLQAAIALKKKGFTTC | 120 120 120 102 |
| Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238) | ILTNTWLDDRAERDGLAQLMCELKMHFDFLIESCQVGMVKIVTNNWLDDSDKRDILAQMMCELSQHFDFLIESCQVGMIKIVTNNWLDDGDKRDSLAQMMCELSQHFDFLIESCQVGMIK | 160 160 160 142 |
| Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238) | PEPQIYKFLLDTLKASPSEVVFLDDIGANLKPARDLGMVTPEPQIYKFVLDTLKAKPNEVVFLDDFGSNLKPARDMGMVTPEPQIYNFLLDTLKAKPNEVVFLDDFGSNLKPARDMGMVTPEPQIYNFLLDTLKAKPNEVVFLDDFGSNLKPARDMGMVT | 200 200 200 182 |
| Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238) | ILVQDTDTALKELEKVTGIQLLNTPAPLPTSCNPSDMSHGILVRDTASALRELEKVTGTQFPEAPLPVPCSPNDVSHGILVHNTASALRELEKVTGTQFPEAPLPVPCNPNDVSHGILVHNTASALRELEKVTGTQFPEAPLPVPCNPNDVSHG | 240 238 238 220 |
| Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238) | Y V T V K P R V R L H F V E L G S G P A V C L C H G F P E S W Y S W R Y Q I P A Y V T V K P G I R L H F V E M G S G P A L C L C H G F P E S W F S W R Y Q I P A Y V T V K P G I R L H F V E M G S G P A L C L C H G F P E S W F S W R Y Q I P A Y V T V K P G I R L H F V E M G S G P A L C L C H G F P E S W F S W R Y Q I P A | 279 278 278 260 |
| Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238) | LAQAGFRVLAIDMKGYGESSAPPEIEEYCMEVLCKEMVTF LAQAGFRVLAIDMKGYGDSSSPPEIEEYAMELLCEEMVTF LAQAGFRVLAIDMKGYGDSSSPPEIEEYAMELLCKEMVTF LAQAGFRVLAIDMKGYGDSSSPPEIEEYAMELLCKEMVTF | 319 318 318 300 |
| Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238) Protein sequences obtained from | LDKLGLSQAVFIGHDWGGMLVWYMALFYPERVRAVASLNTLNKLGIPQAVFIGHDWAGVLVWNMALFYPERVRAVASLNTLDKLGIPQAVFIGHDWAGVMVWNMALFYPERVRAVASLNTLDKLGIPQAVFIGHDWAGVMVWNMALFYPERVRAVASLNTLDKLGIPQAVFIGHDWAGVMVWNMALFYPERVRAVASLNTnthe NCBI database (accession numbers) showing identical (black) and | 359 358 358 340 |
| | | |

homologous (gray) residues in the mammalian proteins. Sites for primary (†), secondary (‡) and tertiary (°) pharmacophores are indicated above each sequence.

Applicant: Bruce D. Hammock et al Title: IMPROVED INHIBITORS FOR THE SOLUBLE EPOXIDE HYDROLASE

> Sheets 4 of 11 Attorney Docket: 02307W-131010US

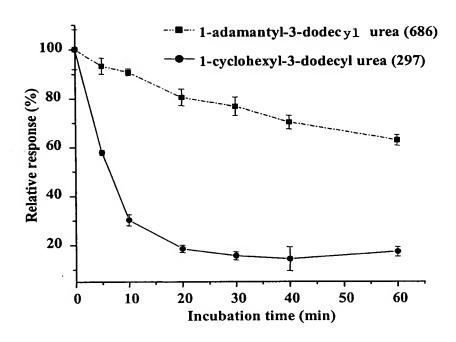
Figure 5

| | 11 | |
|--|--|--------------------------|
| Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238) | PFIPANPNMSPLESIKANPVFDYQLYFQEPGVAEAEL EQNPLMPPNPEVSPMEVIRSIPVFNYQLYFQEPGVAEAEL EKNPFMPPDPDVSPMKVIRSIPVFNYQLYFQEPGVAEAEL EKNPFMPPDPDVSPMKVIRSIPVFNYQLYFQEPGVAEAEL EKN | 399 398 398 380 |
| Human sEH (JC4711) Rat sEH (P80299) Mouse liver sEH (AAA37555) Mouse ovary sEH (AAM28238) | LSRTFKSLFRASDESVLSM-HKVCEAGGLFVNSPEEPSLS MSRTFKSFFRASDETGFIAVHKATEIGGILVNTPEDPNLS MSRTFKSFFRASDETGFIAVHKATEIGGILVNTPEDPNLS MSRTFKSFFRASDETGFIAVHKATEIGGILVNTPEDPNLS | 438 438 438 420 |
| Human sEH (JC4711) | RMVTEEEIQFYVQQFKKSGFRGPLNWYRNMERNWKWA CKS | 478 |
| Rat sEH (P80299) | KITTEEEIBYYIQQFKKSGFRGPLNWYRNTERNWKWS CKA | 478 |
| Mouse liver sEH (AAA37555) | KITTEEEIBFYIQQFKKTGFRGPLNWYRNTERNWKWS CKG | 478 |
| Mouse ovary sEH (AAM28238) | KITTEEEIBFYIQQFKKTGFRGPLNWYRNTERNWKWS CKG | 460 |
| Human sEH (JC4711) | LGRKILIPALMVTAEKDFVLVPQMSQHMEDWIPHLKRGHI | 518 |
| Rat sEH (P80299) | LGRKILVPALMVTAEKDIVLRPEMSKNMENWIPFLKRGHI | 518 |
| Mouse liver sEH (AAA37555) | LGRKILVPALMVTAEKDIVLRPEMSKNMEKWIPFLKRGHI | 518 |
| Mouse ovary sEH (AAM28238) | LGRKILVPALMVTAEKDIVLRPEMSKNMEKWIPFLKRGHI | 500 |
| Human sEH (JC4711) | EDCGHWTQMDKPTEVNQILIKWLDSDARNPPVVSKM | 554 |
| Rat sEH (P80299) | EDCGHWTQIEKPAEVNQILIKWLKTEIQNPSVTSKI | 554 |
| Mouse liver sEH (AAA37555) | EDCGHWTQIEKPTEVNQILIKWLQTEVQNPSVTSKI | 554 |
| Mouse ovary sEH (AAM28238) | EDCGHWTQIEKPTEVNQILIKWLQTEVQNPSVTSKI | 536 |

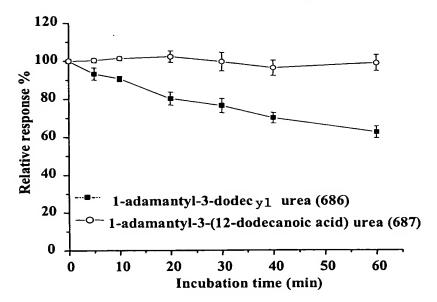
Protein sequences obtained from the NCBI database (accession numbers) showing identical (black) and homologous (gray) residues in the mammalian proteins. Sites for primary (†), secondary (‡) and tertiary (°) pharmacophores are indicated above each sequence.

Applicant: Bruce D. Hammock et al
Title: IMPROVED INHIBITORS FOR THE SOLUBLE EPOXIDE
HYDROLASE
Sheets 5 of 11

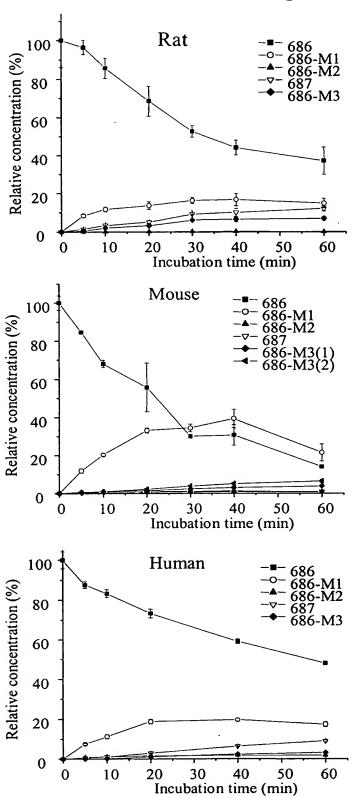
Sheets 5 of 11 Attorney Docket: 02307W-131010US







Applicant: Bruce D. Hammock et al Title: IMPROVED INHIBITORS FOR THE SOLUBLE EPOXIDE **HYDROLASE** Sheets 6 of 11 Attorney Docket: 02307W-131010US



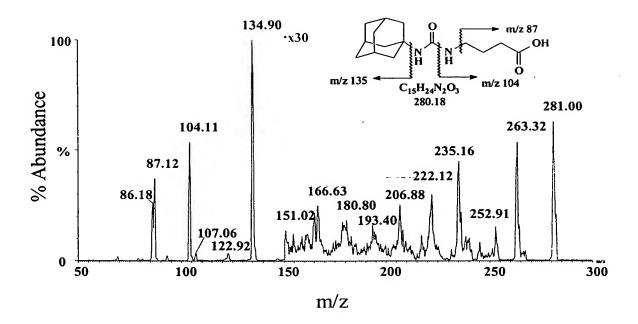
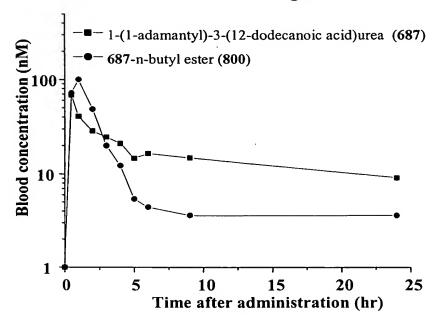
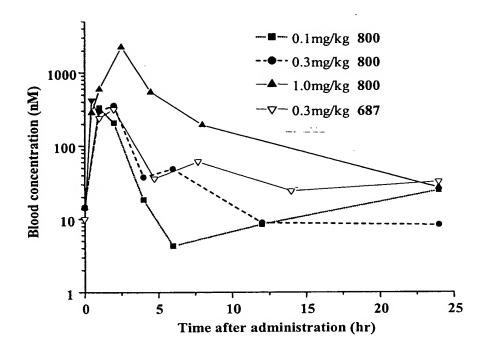


Figure 10



Applicant: Bruce D. Hammock et al
Title: IMPROVED INHIBITORS FOR THE SOLUBLE EPOXIDE
HYDROLASE
Shoots 8 of 11

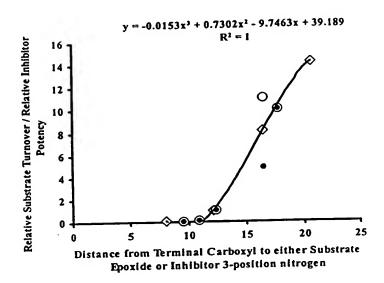
Sheets 8 of 11 Attorney Docket: 02307W-131010US



Applicant: Bruce D. Hammock et al
Title: IMPROVED INHIBITORS FOR THE SOLUBLE EPOXIDE
HYDROLASE
Sheets 9 of 11
Attorney Docket: 02307W-131010US

Applicant: Bruce D. Hammock et al Title: IMPROVED INHIBITORS FOR THE SOLUBLE EPOXIDE HYDROLASE

Sheets 10 of 11 Attorney Docket: 02307W-131010US

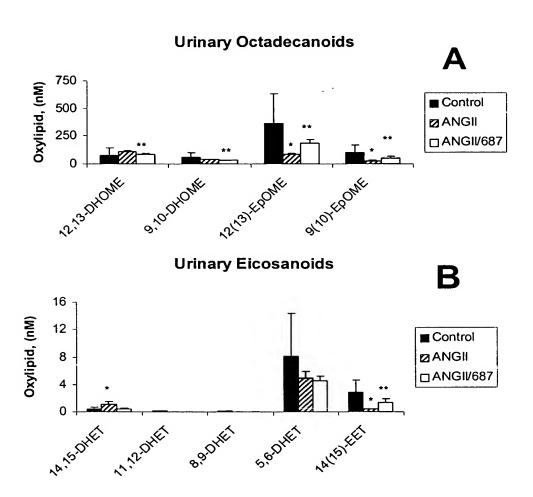


- ♦ Relative EET Turnover
- O Inhibitor Rank-order potency with Ms EH
- Inhibitor Rank-order potency with HsEH

Applicant: Bruce D. Hammock et al
Title: IMPROVED INHIBITORS FOR THE SOLUBLE EPOXIDE
HYDROLASE
Sheets 11 of 11

Sheets 11 of 11 Attorney Docket: 02307W-131010US

Figure 14



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